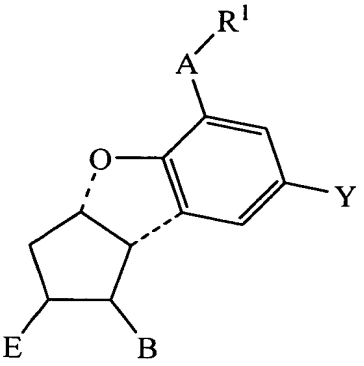
CLAIMS

1. An enhancing agent for enhancing therapeutic or prophylactic effect of administering (a) renin-angiotensin system inhibitor(s) on (a) renal disease(s), comprising as an effective ingredient a prostaglandin I derivative represented by the Formula (I):



(I)

[wherein R^1 is

(A) $COOR^2$, wherein R^2 is

hydrogen or a pharmaceutically acceptable cation,

2) C_1-C_{12} straight alkyl or C_3-C_{14} branched alkyl,

Z-R^3, wherein Z is covalent bond, or straight or branched alkylene represented by C_tH_{2t} wherein t is an integer of 1 to 6, R^3 is C_3-C_{12} cycloalkyl or C_3-C_{12} cycloalkyl substituted with 1 to 3 R^4(s) wherein R^4 is hydrogen or C_1-C_5 alkyl,

$-(CH_2CH_2O)_nCH_3$, wherein n is an integer of 1 to 5,

-Z-Ar^1, wherein Z represents the same meanings described above, Ar^1 is phenyl, α-naphthyl, β-naphthyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, α-furyl, β-furyl, α-thienyl, β-thienyl or substituted phenyl (wherein the substituent(s) is(are) at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, C_1-C_4 alkyl, nitro, cyano, methoxy, phenyl, phenoxy, p-acetamidebenzamide, $-CH=N-NH-C(=O)-NH_2$, $-NH-C(=O)-Ph$, $-NH-C(=O)-CH_3$ and $-NH-C(=O)-NH_2$),

$-C_tH_{2t}COOR^4$, wherein C_tH_{2t} and R^4 represent the same meanings as described above,

$-C_tH_{2t}N(R^4)_2$, wherein C_tH_{2t} and R^4 represent the same meanings as described above,

$-CH(R^5)-C-(=O)-R^6$, wherein R^5 is hydrogen or benzoyl, and R^6 is phenyl, p-bromophenyl, p-chlorophenyl, p-biphenyl, p-nitrophenyl, p-benzamidephenyl or 2-naphthyl,

$-C_pH_{2p}-W-R^7$, wherein W is -CH=CH-, $-CH=CR^7-$ or $-C\equiv C-$, wherein R^7 is hydrogen, C_1-C_{30} straight or branched alkyl or C_1-C_{30} aralkyl, p is an integer of 1 to 5, or

10) $-CH(CH_2OR^8)_2$, wherein R^8 is C_1-C_{30} alkyl or acyl,

(B) $-CH_2OH$,

(C) $-C(=O)N(R^9)_2$, wherein R^9 is hydrogen, C_1-C_{12} straight alkyl, C_3-C_{12} branched alkyl, C_3-C_{12} cycloalkyl, C_4-C_{13} cycloalkylalkylene, phenyl, substituted phenyl (wherein the definitions of the substituent(s) are the same as those described in (A) 5) mentioned above), C_7-C_{12} aralkyl or $-SO_2R^{10}$ wherein R^{10} is C_1-C_{10} alkyl, C_3-C_{12} cycloalkyl, phenyl, substituted phenyl (wherein the definition(s) of the substituent(s) is(are) the same as those described in (A) 5) mentioned above), or C_7-C_{12} aralkyl, wherein the two R^9s may be the same or different, with the proviso that when one of them is $-SO_2R^{10}$, the other R^9 is not $-SO_2R^{10}$, or

(D) $-CH_2OTHP$ (wherein THP is tetrahydropyranyl),

A is

$-(CH_2)_m-$,

$-CH=CH-CH_2-$,

$-CH_2-CH=CH-$,

$-CH_2-O-CH_2-$,

-CH=CH-,

$-O-CH_2-$ or

7) $-C\equiv C-$, wherein m is an integer of 1 to 3,

Y is hydrogen, C_1-C_4 alkyl, chlorine, bromine, fluorine, formyl, methoxy or nitro,

B is -X-C(R^{11})(R^{12})OR^{13}, wherein R^{11} is hydrogen or C_1-C_4 alkyl, R^{13} is hydrogen, C_1-C_{14} acyl, C_6-C_{15} aroyl, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl or t-butyl,

X is

-CH_2-CH_2-

-CH=CH- or

-C≡C-,

R^{12} is

C_1-C_{12} straight alkyl, C_3-C_{14} branched alkyl,

-Z-Ar^2, wherein Z represents the same meanings as described above, Ar^2 is phenyl, α-naphthyl, β-naphthyl, or phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, C_1-C_4 alkyl, nitro, cyano, methoxy, phenyl and phenoxy,

-C_tH_{2t}OR^{14}, wherein C_tH_{2t} represents the same meanings as described above, R^{14} is C_1-C_6 straight alkyl, C_3-C_6 branched alkyl, phenyl, phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, C_1-C_4 alkyl, nitro, cyano, methoxy, phenyl or phenoxy-substituted phenyl, cyclopentyl, cyclohexyl, cyclopentyl substituted with 1 to 4 C_1-C_4 straight alkyl and cyclohexyl substituted with 1 to 4 C_1-C_4 straight alkyl,

-Z-R^3, wherein Z and R^3 represent the same meanings as mentioned above,

-C_tH_{2t}-CH=C(R^{15})R^{16}, wherein C_tH_{2t} represents the same meanings as mentioned above, R^{15} and R^{16} represent hydrogen, methyl, ethyl, propyl or butyl, or

6) -C_uH_{2u}-C≡C-R^{17}, wherein u is an integer of 1 to 7, C_uH_{2u} is straight or branched alkylene, and R^{17} is C_1-C_6 straight alkyl,

E is hydrogen or -OR^{18}, wherein R^{18} is C_1-C_{12} acyl, C_7-C_{15} aroyl or R^2 (wherein R^2 represents the same meanings as described above),

said formula includes d-isomers, l-isomers and racemic compounds].

2. The enhancing agent according to claim 1, wherein in said Formula (I),

R^1 is $COOR^2$,

wherein R^2 is hydrogen or a pharmaceutically acceptable cation,

A is

1) $-(CH_2)_m-$

2) $-CH_2-CH=CH-$

wherein m is an integer of 1 to 3,

Y is hydrogen,

B is $-X-C(R^{11})(R^{12})OR^{13}$,

wherein R^{11} and R^{13} is hydrogen, X is

1) $-CH=CH-$

2) $-C\equiv C-$,

R^{12} is

1) $-Z-Ar^2$

wherein Z is covalent bond, or straight or branched alkylene represented by C_tH_{2t} wherein t is an integer of 1 to 6, Ar^2 is phenyl, α-naphthyl, β-naphthyl, or phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, C_1-C_4 alkyl, nitro, cyano, methoxy, phenyl and phenoxy, or

2) $-Z-R^3$

wherein Z represents the same meanings as described above, R^3 is C_3-C_{12} cycloalkyl, or

3) $-C_uH_{2u}-C\equiv C-R^{17}$

wherein u is an integer of 1 to 7, C_uH_{2u} is straight or branched alkylene, and R^{17} is C_1-C_6 straight alkyl,

said formula includes d-isomers, l-isomers and racemic compounds.

3. The enhancing agent according to claim 1, wherein in said Formula (I),

R^1 is $COOR^2$, wherein R^2 is hydrogen or a pharmaceutically acceptable cation,

A is $-(CH_2)_m-$, wherein m is an integer of 1 to 3,

Y is hydrogen,

B is $-X-C(R^{11})(R^{12})OR^{13}$, wherein R^{11} and R^{13} is hydrogen,

X is -CH=CH-,

R^{12} is $-C_uH_{2u}-C\equiv C-R^{17}$, wherein u is an integer of 1 to 7, C_uH_{2u} is straight or branched alkylene, and R^{17} is C_1-C_6 straight alkyl,

E is hydrogen or $-OR^{18}$, wherein R^{18} is R^2 (wherein R^2 represents the same meanings as described above),

said formula includes d-isomers, l-isomers and racemic compounds.

4. The enhancing agent according to claim 1, wherein said prostaglandin I derivative is beraprost or pharmaceutically acceptable salt or ester thereof.

5. The enhancing agent according to any one of claims 1 to 4, wherein said renin-angiotensin system inhibitor is an ACE inhibitor.

6. The enhancing agent according to claim 5, wherein said ACE inhibitor is selected from the group consisting of enalapril maleate, alacepril, delapril, ramipril, captopril, lisinopril, benazepril hydrochloride, libenzapril, quinaprilat, imidapril hydrochloride, zofenopril calcium, fosinopril sodium, cilazapril, temocapril hydrochloride, spirapril hydrochloride, perindopril erbumine, moexipril hydrochloride, trandolapril, ceronapril hydrate, utibapril, omapatrilat, Sampatrilat, and their pharmaceutically acceptable salts.

7. The enhancing agent according to any one of claims 1 to 4, wherein said renin-angiotensin system inhibitory substance is a compound having antagonistic action against angiotensin II receptor.

8. The enhancing agent according to claim 7, wherein said compound having antagonistic action against angiotensin II receptor is selected from the group consisting of losartan, eprosartan, candesartan cilexetil, valsartan, telmisartan, irbesartan, tasosartan, olmesartan medoxomil, EXP-3174, zolasartan, saprisartan,

elisartan potassium, ripisartan, milfasartan, forasartan, embusartan, fonsartan, E4177, YM358, ICI-D8731, TAK-536, CL-329167, pomisartan, candesartan, and their pharmaceutically acceptable salts.

9. The enhancing agent according to claim 8, wherein said compound having antagonistic action against angiotensin II receptor is selected from the group consisting of losartan, eprosartan, candesartan cilexetil, valsartan, telmisartan, irbesartan, tasosartan, olmesartan medoxomil, EXP-3174, zolasartan, saprisartan, embusartan, candesartan, and their pharmaceutically acceptable salts.

10. The enhancing agent according to any one of claims 1 to 9, wherein said renal disease is diabetic nephropathy, glomerulonephritis, interstitial nephritis, acute renal failure, or chronic renal failure.

11. The enhancing agent according to claim 9, wherein said renal disease is chronic renal failure.

12. The enhancing agent according to any one of claims 1 to 11, wherein said effect of administering renin-angiotensin system inhibitor is the effect to suppress elevation of serum creatinine with time during said renal disease(s).

13. The enhancing agent according to any one of claims 1 to 11, wherein said effect of administering renin-angiotensin system inhibitory substance is the effect to suppress sequential decrease in the reciprocal of serum creatinine with time.

14. The enhancing agent according to any one of claims 1 to 11, wherein said effect of administering renin-angiotensin system inhibitor is the effect to suppress decrease in the glomerular filtration rate with time during said renal disease(s).

15. A therapeutic or prophylactic agent for renal disease, comprising as effective ingredients the enhancing agent according to any one of claims 1 to 14 and a renin-angiotensin system inhibitor.

16. A kit for therapy or prophylaxis for renal diseases, comprising separately the enhancing agent according to any one of claims 1 to 14, and a drug containing as an

effective ingredient a renin-angiotensin system inhibitor, wherein said kit is for administering the enhancing agent and the renin-angiotensin system inhibitor at the same time or at different times.

17. A method for enhancing therapeutic or prophylactic effect of renin-angiotensin system inhibitor on renal disease, comprising administering the enhancing agent according to any one of claims 1 to 14 to a patient to whom (a) rennin-angiotensin system inhibitor(s) is(are) administered.

18. A method for treating or preventing a renal disease, comprising administering said therapeutic or prophylactic agent for renal diseases according to claim 15, or the drugs contained in the kit of therapeutic or prophylactic agents for renal diseases according to claim 16.

19. Use of said prostaglandin I derivative recited in any one of claims 1 to 4, for the production of an agent for enhancing the therapeutic or prophylactic effect of administering the renin-angiotensin system inhibitor on renal diseases.

20. The use according to claim 19, wherein said enhancing agent is the enhancing agent according to any one of claims 5 to 14.